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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,281	12/21/2001	John Wyrick	10050560-1	4057

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AGILENT TECHNOLOGIES INC.
INTELLECTUAL PROPERTY ADMINISTRATION,LEGAL DEPT.
MS BLDG. E P.O. BOX 7599
LOVELAND, CO 80537

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/032,281	WYRICK ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,15-17,87,88 and 90-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,15-17,87,88 and 90-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The rejection of claims 1-6, 8, 15-17, 87, 88 and 90-92 under 35 U.S.C. 112, first paragraph is withdrawn in view of the amendment.

Claim Interpretation

2. Several of the terms in the claims lack specific definitions in the specification and are broadly interpreted. The term "intergenic" is interpreted as any region in the genome which is "between two genes" where a gene is an open reading frame. The term "microarray" is simply any substrate with which a nucleic acid can be hybridized and can include a southern blot.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-6, 8, 15-17, 87, 88 and 90-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strutt et al (EMBO J. (1997) 16(12):3621-3631) in view of Schena (Tibtech (1998) 16:301-306).

Strutt teaches a method of claim 1 for *identifying a region of a genome of a cell to which a protein of interest binds* (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see page 3622, column 1 and page 3630, column 2, subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin"),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), by sonication, thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see page 3622, column 2 and page 3630, column 2, subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin", where it is indicated that the DNA was sonicated),

c) removing a DNA fragment to which the protein of interest is bound from a first portion the mixture produced in b) (see page 3622, column 1 and page 3630, column 2, subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin", where antibodies were used to remove the DNA fragment),

d) separating the DNA fragment identified in c) from the protein of interest (see page 3622, column 1 and page 3631, column 1, under subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin"),

e) labeling the DNA fragment of d) with a first label by:

i. blunting said DNA fraqment to produce blunt ends;

ii. ligating adaptors to said blunt ends;

iii. amplifying said DNA fragment using a primer that binds to said adaptors; and

iv. labelinq said DNA fragment either durinq or after said amplifying to produce a labeled DNA fragment (see page 3622, where Strutt teaches that the sonicated DNA had blunt ends and that blunt end linkers were ligated to the blunt ends, followed by amplification using the primers and see page 3631, column 2, where amplified DNA was labeled radioactively (see page 3623, figure 1)),

f) labeling a second portion of the mixture produced in b) with a label to produce a second sample (see page 3622, column 2, where Strutt expressly teaches the use of control immunoprecipitations from the sample of b) as well as figure 1, which shows a control immunoprecipitation compared to the specific PC and GAGA immunoprecipitations).

g) combining the labeled DNA fragment of e) and the second sample of f) with a DNA microarray (see figure 1 and page 3631, column 1, where a Southern blot is a type of DNA microarray) *which comprises sequences that detect intergenic regions,*

under conditions in which nucleic acid hybridization occurs (see figure 1 and figure 2, where hybridization clearly occurs throughout the region including in locations that are between genes as shown by figure 2, such as in the iab5 region),

h) comparing results obtained from said first label to results obtained from said second sample to identify the sequences of g) to which the DNA fragment hybridizes, whereby the region identified in h) is the region of the genome in the cell to which the protein of interest binds (see figure 1, figure 2 and page 3622, column 2, where Strutt teaches a comparison of the control to the sample to identify the region in which the proteins of interest bind).

With regard to claims 1, Strutt teaches hybridization to a southern blot, which is a type of microarray as discussed above (see figure 1).

With regard to claims 2 Strutt teaches the use of Drosophila melanogaster cells which are eukaryotic (see page 3630, column 1).

With regard to claims 3, Strutt teaches the use of DNA binding transcription factors (see page 3621, columns 1 and 2).

With regard to claims 4, Strutt teaches crosslinking with formaldehyde (see page 3630, column 2).

With regard to claims 5, Strutt teaches the use of antibodies to bind the protein of interest (see page 3630, column 2).

With regard to claims 6, 90 and 91, Strutt teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see page 3631, column 1).

With regard to claims 8, Strutt teaches the use of a control (see 3623, figure 1).

With regard to claims 17, Strutt teaches shearing the DNA to make fragments (see page 3622, column 1).

With regard to claims 87, Strutt teaches identifying a DNA binding site of the protein where the protein is a transcription factor (see figure 4).

With regard to claim 88, Strutt teaches sequences that are located over a region of the Drosophola chromosome (see figure 2).

Strutt does not teach the use of two colors of fluorescent labels to compare the control and test samples in the place of the radioactive samples and Strutt does not teach a traditional "microarray", teaching only the use of Southern blots.

Schena teaches the use of two colors of fluorescent labels to multiplex samples on microarrys (see page 301 to page 302).

With regard to claims 15 and 16, Schena expressly teaches fluorescent labeling, showing a Cy5 fluorescently labeled microarray in figure 3.

Schena teaches the use of microarrays to analyze genomic information (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent labels of Schena for the radioactive labels of Strutt since Schena expressly indicates that fluorescent labeling is advantageous since "Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating

complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)." This same logic would apply to the method of Strutt, since while Strutt does perform the hybridization to the same support, the hybridization does not occur at the same time under precisely the same reaction conditions, and an ordinary practitioner would recognize, from the motivation of Schena, that the use of two fluorescent labels would permit multiplexing the analysis under precisely the same conditiosn, eliminating many of the complicating factors in the analysis. Further, an ordinary practitioner would have been motivated to perform the substitution of the microarrays of Schena for the Southern blot of Strutt since Schena expressly notes "Although reminiscent of filter based assays, chip assays are a fundamental departure from techniques that employ porous membranes. Chips allow true parallelism, miniaturization, multiplexing and automation, and these key features provide a set of performance specifications that cannot be achieved with the earlier technologies (see page 301, column 2)." Schena is expressly teaching that chip assays are superior to the prior art filter based assays such as Southern blots of Orlando. Schena provides significant additional motivation to use microarrays in the place of such filter based assays noting,

> "Microarray assays allow massive parallel data acquisition and analysis. Parallelism greatly increases the speed of experimental progress and allows meaningful comparisons to be made between the genes or gene products represented in the microarray. Microarray assays may eventually allow the analysis of the entire human genome in a single reaction, and recent gene-expression experiments in yeast represent an important step towards this goal. Miniaturization of conventional assays is a general trend in biomedical research. Microscale assays reduce reagent consumption, minimize reaction volumes, increase the sample

> concentration and accelerate the reaction kinetics. Chip-based assays allow sensitive and rapid data detection with either confocal scanners or cameras equipped with charged-coupled devices. Although current microarray assays focus on nucleic acid hybridization, future studies will undoubtedly involve the parallel analysis of proteins, lipids, carbohydrates and small molecules. Multiplexing, the process by which multiple samples are analysed in a single assay, is another enabling feature of the microarray approach. Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)."

An ordinary practitioner, motivated by Strutt to analyze genomic nucleic acids in order to identify regions of protein binding, would have been motivated by Schena to substitute the use of a microarray for the southern blot since Schena teaches that microarrays are faster, provide more meaningful comparisons, reduce reagent consumption and accelerate reaction kinetics, as well as increasing accuracy as discussed by Schena above.

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Strutt to the entire genome, as required by claims 88 and 92, in order to analyze the location of transcription factors on the entire genome simultaneously. This is particularly obvious in light of Schena, who teaches analysis of genomic samples.

The ordinary practitioner is highly skilled in this art, at least a Ph.D. with years of experience as evidenced by the authors of the prior art. Dr. Schena is world renowned with a Ph.D. and 20 years of experience, Dr. Helen Strutt was a Ph.D. with years of

postdoctoral experience. Dr. Giacomo Cavalli was a Ph.D. with years of postodoctoral experience. Dr. Renato Paro is a Ph.D. with more than 20 years experience who was a professor of molecular biology. Given this high level of skill, the use of a two color control on a microarray would have been prima facie obvious to these ordinary practitioners at the time of the invention.

Response to Declaration

6. The Wyrick Declaration under 37 CFR 1.132 filed May 15, 2007 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 103 as set forth in the last Office action because:

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion.

(1) In the instant case, the nature of the fact sought to be established is whether or not it is prima facie obvious to use the fluorescent labels and microarray of Schena in the method of Strutt. This is a legal conclusion based upon the factors in Graham v. John Deere. The conclusion in the rejection is based upon the evidence of the Strutt and Schena references.

(2) There is significant evidence which opposes the conclusion of the Wyrick declaration. Dr. Wyrick states that the sonication, blunting, ligation and amplifying was unexpected. This is the precise labeling method performed by Strutt and was anticipated by Strutt. There is nothing unexpected in this being superior since Strutt

expressly notes that the method is improved by using blunt ended ligation because it will give a more random size distribution of the fragments (see page 3622, column 1).

(3) Dr. Wyrick is the inventor and therefore has a direct interest in the case.

(4) There is no factual support for Dr. Wyrick's conclusion that any improvement was unexpected. Strutt performed the method prior to Dr. Wyrick and obtained the same result which Dr. Strutt had expected.

It is therefore concluded that the Wyrick declaration does not overcome the case of prima facie obviousness.

Response to Arguments

7. Applicant's arguments filed November 28, 2006 have been fully considered but they are not persuasive.

Many of Applicant's arguments are moot in view of the new grounds of rejection necessitated by this amendment. A few arguments remain applicable.

Applicant argues that the result is unexpected because sonicated methods with direct ligation, rather than the use of restriction enzymes, are argued to provide a better representation of the genome. That method step and that result are precisely performed by Strutt, who therefore rebuts both the argument and addresses the claim limitation in noting that the use of a random size distribution will result in an improved assay (see page 3622, columns 1 and 2).

Applicant argues that the prior art falls because neither Orlando nor Mercola teach second sample which is a "non immunoprecipitated sample". Strutt does not teach a "non immunoprecipitated sample" either. However, there is no such limitation in

the claims. Claim 1 does not require that the second sample is a "non immunoprecipitated" sample. It simply requires that a second portion is labeled. At no point does claim 1, or any of the other claims, require or indicate that the sample is not immunoprecipitated.

Applicant disagrees with the level of skill in the art. The level of skill can only be measured by those who work in the art, not someone else who does not work in the art. Therefore, applicant's arguments lack any evidentiary basis to rebut the skill level, which is based upon the skill level of authors of the papers of those who were working in the art at the time the invention was made.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

9/5/07